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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,915	05/10/2005	Gerd Haberhausen	21719-US	9560

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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,915	HABERHAUSEN ET AL.	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/27/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on June 27, 2008 is acknowledged and has been entered. Claim 1 has been amended. Claims 8-9 have been canceled. Claims 1-7 are pending.

Claims 1-7 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made NON-FINAL.

Previous Grounds of Rejection

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2 and 6 of copending Application No. 10/534955 ('955 application) in view of Jannes et al. (WO96/00298; January 1996).

While these claims are not identical, they are not patentably distinct from one another. The claims of the copending '955 application are directed to a method for identification of a Gram positive pathogenic organism comprising amplification of a clinical sample, detecting amplification through hybridization, monitoring hybridization and identifying the organism(s). The claims of the instant application as amended are directed to a more narrow method of amplification and detection of pathogenic organisms comprising detection of a specific rRNA spacer region. In the copending application, claim 6 recites the detection of an rRNA spacer region. While the copending application does not specify the specific rRNA spacer sequence as comprising either 16S/23S or 18S/26S rRNA sequences, Jannes teaches specific detection of 16S/23S rRNA sequences. Considering the teaching by Jannes, "the spacer region situated between the 16S rRNA and the 23S rRNA gene, also referred to as the internal transcribed spacer (ITS), is an advantageous target region for probe development for detection of pathogens of bacterial origin" (p. 1-2), therefore it would have been prima facie obvious that 16S/23S or 18S/26S rRNA sequences fall within the scope of the rRNA sequences claimed in the copending application.

Furthermore, in the instant application, gram positive bacteria are detected, however this limitation is recited as a dependent claim and as part of a method that comprises identification of both gram negative and gram positive bacteria. The similarities between these two copending applications, including the steps of monitoring temperature dependence of hybridization and using this hybridization detection to identify specific organisms, render the method of the instant application obvious.

This is a provisional obviousness-type double patenting rejection.

3. Claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/532319 ('319 application). While these claims are not identical, they are not patentably distinct from one another. The claims of the copending '319 application are directed to a method for detecting the presence of bacterial pathogens in clinical samples, comprising steps directed to the isolation of nucleic acids, amplification and quantifying the amount of nucleic acids comprising a sequence that is specific for a bacterial pathogen, wherein the method of quantification comprises amplification, monitoring of amplification through a hybridization probe and through monitoring temperature dependence of hybridization. The claims of the instant application are directed to a similar method directed to the amplification and detection of bacterial pathogens. The differences between the current application and the '319 application lie in the specific recitation of analysis of specific aliquots of clinical specimens and comprising the use of multiple hybridization reagents in the instant application as contrasted with the real-time monitoring of amplification in the copending application, which falls within the scope of the amplification,

detection and monitoring of temperature dependence of hybridization in the instant application. While the copending '319 application does not recite 16S/23S or 18S/26S rRNA spacer sequence, this preselected sequence of the instant application falls within the scope of the claim as recited in the copending application. Furthermore, while the copending application does not specify the specific rRNA spacer sequence as comprising either 16S/23S or 18S/26S rRNA sequences, Jannes teaches specific detection of 16S/23S rRNA sequences. Considering the teaching by Jannes, "the spacer region situated between the 16S rRNA and the 23S rRNA gene, also referred to as the internal transcribed spacer (ITS), is an advantageous target region for probe development for detection of pathogens of bacterial origin" (p. 1-2), therefore it would have been prima facie obvious that 16S/23S or 18S/26S rRNA sequences fall within the scope of the rRNA sequences claimed in the copending application.

This is a provisional obviousness-type double patenting rejection.

New Grounds of Rejection

Information Disclosure Statement

The information disclosure statement (IDS) submitted on June 27, 2008 was filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 103

4. Claims 1-4 and 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loeffler et al. (Diagnostic Microbiology and Infectious Disease, 2000, vol. 38, p. 207-212) in view of Chang et al. (Journal of Clinical Microbiology, 2001, vol. 39, no. 10, p. 3466-3471) and de Silva et al. (Biochemica, 1998, no. 2, p. 12-15). Loeffler teaches a method of amplification and detection of pathogenic organisms through the detection of the 18S rRNA gene (Abstract).

With regard to claim 1, Loeffler teaches a method for identification of a pathogenic organism from a predetermined group of pathogens, comprising:

a) at least partially purifying nucleic acid from a clinical sample (p. 208, col. 1, where multiple clinical samples were present; 'DNA extraction' heading, where DNA was extracted prior to analysis of the samples),

b) subjecting at least a first aliquot of said clinical specimen to at least a first amplification and detection reaction comprising:

ba) an amplification step using at least a first set of amplification primers capable of amplifying a pre-selected nucleic acid sequence from several or all members of said predetermined group of pathogens, wherein said predetermined group of pathogens comprises members of two or more genera (p. 208, col. 1, where samples were amplified using primers designed to detect the 18S rRNA gene; Abstract, Table 1, where a variety of predetermined pathogens of two or more genera are amplified and detected),

bb) a detection step using a plurality of hybridization reagents, said reagents together being capable of specifically detecting a pre-selected nucleic acid sequence comprising the region from all members of said predetermined group of pathogens (Table 1, where species specific and

candida specific probes are listed), said detection step comprising:

bba) monitoring hybridization of each of said hybridization reagents at a pre-selected temperature, said hybridization being indicative for at least the genus of said pathogen present in the sample (Figure 3, where the different samples comprise clinical isolates and they are hybridized to a plurality of oligonucleotide probes from a variety of genera), and wherein said amplification and detection reaction is indicative of the identity of said pathogenic organism from a predetermined group of pathogens (Figure 3, where the results indicate the detection and identification of the pathogenic organism).

With regard to claim 2, Loeffler teaches an embodiment of claim 1, further comprising subjecting at least a second aliquot of said clinical specimen to at least a second amplification and detection reaction in a different reaction vessel from said first aliquot of said clinical specimen being subjected to said first amplification and detection reaction in two different reaction vessels (p. 208, where multiple clinical samples were analyzed and where each individual specimen would be analyzed by amplification and detection in a separate aliquot and a separate reaction vessel).

With regard to claim 3, Loeffler teaches an embodiment of claim 2, further comprising subjecting at least a third aliquot of said clinical specimen to at least a third amplification and detection reaction in a different reaction vessel from said first aliquot of said clinical specimen being subjected to said first amplification and detection reaction, and said second aliquot of said clinical specimen being subjected to said second amplification and detection reaction (p. 208, where multiple clinical samples were analyzed and where each individual specimen would be analyzed by amplification and detection in a separate aliquot and a separate reaction vessel).

With regard to claim 4, Loeffler teaches an embodiment of claim 1, further comprising a hybridization reagent capable of specifically detecting an internal control (p. 208, col. 2, 'controls' heading, where genomic DNA from candida species were included).

With regard to claim 6, Loeffler teaches an embodiment of claim 3, wherein fungal pathogens are exclusively identified in said third amplification and detection reaction (Abstract, Table 1, where all of the pathogens identified are fungal pathogens).

With regard to claim 7, Loeffler teaches an embodiment of claim 2, wherein said first amplification and detection reaction and said second amplification and detection reaction are performed with the same thermocycling profile (p. 208, where the amplification reaction conditions applied to each of the clinical samples are the same, even if they are amplified and detected in the same or separate reaction vessels).

Regarding claim 1, Loeffler does not teach that the primers target the spacer region between 18S and 26S rRNA. Chang teaches identification of species and strains using analysis of ribosomal RNA spacer regions (Abstract).

With regard to claim 1, Chang teaches amplifying a preselected nucleic acid sequence comprising the 18S/26S rRNA spacer region from several or all members of said predetermined group of pathogens (Abstract).

Further regarding claim 1, Loeffler does not explicitly teach step bbb, wherein the temperature dependence of hybridization is monitored as indicative for at least the species of said pathogen. Loeffler also does not teach that amplification and detection occur in the same reaction vessel.

With regard to claim 1, deSilva teaches an embodiment wherein the amplification and detection occur in the same reaction vessel (p. 15, col. 2, where it is again noted that Light Cycler probes are useful for real-time monitoring of PCR amplification reactions and therefore the amplification and real-time detection would have to occur in the same vessel) and teach a method comprising bbb) monitoring temperature dependence of hybridization, said temperature dependence being indicative for at least the species of said pathogen (p. 14, Figures 3 and 5, where an example of monitoring temperature dependence of hybridization is depicted).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Loeffler to target the 18S rRNA spacer sequence of Chang to arrive at the claimed invention with a reasonable expectation for success. As taught by Chang, "yeasts are emerging as important etiological agents of nonsocomial bloodstream infections. A multiplex PCR method was developed to rapidly identify clinically important yeasts that cause fungemia. The method amplified the internal transcribed spacer 1 (ITS1) region between the 18S and 5.8S rRNA genes" (Abstract). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Loeffler to target the 18S rRNA spacer sequence of Chang to arrive at the claimed invention with a reasonable expectation for success.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the methods taught by Loeffler and Chang to incorporate the method of determining and monitoring the temperature dependence of hybridization as taught by deSilva to arrive at the claimed invention with a reasonable expectation for success. While Loeffler teaches standard hybridization and detection of

pathogenic sequences, it would have been prima facie obvious in view of the teachings of deSilva to monitor amplification using melting curve analysis to establish melting temperature as claimed and potentially to apply the sequence specific probes used for detection of the rRNA sequences to the LightCycler format of amplification and detection. As taught by deSilva, "sequence specific monitoring of PCR products is routinely performed by hybridization analysis using blots, gels, or microtiter plates. Hybridization of small oligonucleotide probes to template DNA can be visualized with radioactively labeled probes, fluorescently labeled probes, or chemiluminescent techniques. These techniques, however, are time-consuming and can involve several handling steps that increase the risk of end-product contamination and sample tracking errors". This is in contrast to "Lightcycler is a microvolume fluorometer integrated with a thermal cycler that combines rapid-cycle PCR with real-time fluorescence monitoring" which allows "high throughput genotyping and product quantification" (p. 12). De Silva also teaches, "the ability to monitor PCR product formation in real-time is helpful no matter what fluorescence technique is employed. The advantage of hybridization probes is that real-time hybridization information is available, allowing mutation detection and quantification in the same reaction". Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the methods taught by Loeffler to incorporate the method of determining and monitoring the temperature dependence of hybridization as taught by deSilva to arrive at the claimed invention with a reasonable expectation for success.

5. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Loeffler et al. (Diagnostic Microbiology and Infectious Disease, 2000, vol. 38, p. 207-212) in view of de Silva

et al. (Biochemica, 1998, no. 2, p. 12-15) as applied to claims 1-4 and 6-7 above, and further in view of Jannes et al. (WO96/00298; January 1996, IDS reference). Loeffler teaches a method of amplification and detection of pathogenic organisms through the detection of the 18S rRNA gene (Abstract).

6. Loeffler in view of deSilva teaches all of the limitations of claims 1-4 and 6-7 as recited in the 103 rejection stated above. However, neither Loeffler or de Silva teaches detection of gram positive or negative bacteria.

With regard to claim 5, Jannes teaches an embodiment of claim 2, wherein gram positive pathogenic organisms are exclusively identified by said first amplification and detection reaction, and gram negative pathogenic organisms are exclusively identified by said second amplification and detection reaction (Example 3, p. 78, where Listeria, a gram positive organism is detected; Example 4, p. 84-86, where C. trachomatis, a gram negative organism is detected).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Loeffler, Chang and deSilva to include the targets of gram positive and gram negative bacteria as taught by Jannes to arrive at the claimed invention with a reasonable expectation for success. As taught by Jannes, "the present invention relates to nucleic acid probes derived from the spacer region between 16S and 23S ribosomal ribonucleic acid (rRNA) genes, to be used for the specific detection of eubacterial organisms in a biological sample by a hybridization procedure" (p. 1, lines 3-5). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Loeffler, Jackson and deSilva to include the targets of gram positive and gram

negative bacteria as taught by Jannes to arrive at the claimed invention with a reasonable expectation for success.

Response to Arguments

Applicant's arguments with respect to claims 1-7 have been considered but are moot in view of the new ground(s) of rejection.

Citation of Relevant Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Bialek et al. (Clinical and Diagnostic Laboratory Immunology, 2002, vol. 9, no. 2, p. 461-469) teaches detection of yeast in tissue samples by nested and real-time amplification (Abstract).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephanie K. Mummert/
Examiner, Art Unit 1637